Remarks

Claims 2-3, 6-28, and 30-36, and 38-42 are pending. Claim 2 has been amended. Claim 43 has been added.

Applicants presume that the rejection of claims 2, 17, 19, 21, 23, 25, 32, 34 and 36 under 35 U.S.C. § 112, second paragraph was withdrawn in response to Applicants amendments.

Rejection Under 35 U.S.C. § 112, first paragraph

A. Claims 2-3, 6-28, and 30-36, and 38-42 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. In support of this rejection, the Office Action makes several assertions that constitute factual and legal error.

1. The Office Action alleged that the specification fails to disclose a representative number of species. For example, the Office Action states that besides the proteins encoded by the nucleotide sequence SEQ ID NO:1, the specification fails to disclose any variants of AAV4 Rep and AAV4 Capsid proteins. This is incorrect since the specification and claims disclose amino acids having at least 90% sequence identity to the reference sequence. This is by definition a disclosure of many variants of the proteins. What the Office Action must therefore intend by this statement is that Applicants have allegedly not exemplified any of these variants. This would, however, be legal error as the written description requirement does not require anything more that identifying the metes and bounds of the claim.

2. The Office Action further alleged that "the AAV4 capsid protein variants having at least 90% homology to an amino acid sequence set forth in SEQ ID NO:4 are not associated with any specific functional activity." The Office Action further states that "the variants fail to meet the USPTO written description guidelines because the invention as claimed fails to recite any specific functional limitation associated with structural variants." This is both factually and legally incorrect.

First, written description of a genus of amino acids can be satisfied by reference to percent identity without reciting a function. This is demonstrated in Example 11A of the new

USPTO *Written Description Training Materials* ("Training Materials"; March 25, 2008 Rev. 1), wherein a claim to "an isolated nucleic acid that encodes a polypeptide with at least 85% amino acid sequence identity to SEQ ID NO:2" was concluded to satisfy the written description requirement. The Office Action does not provide any authority for its assertion to the contrary that a specific functional activity associated with the variant is required. Applicants have therefore added new claim 43, which is identical to pending claim 1 but lacking recitation of function. This claim clearly satisfies the written description requirement, since, as pointed out in the Training Materials, "[w]ith the aid of a computer, one of skill in the art could identify all of the nucleic acid sequences ..." (Example 11, page 38, first paragraph).

Second, prior claim 1 did in fact include the functional limitation that "the vector system produces AAV particles." The Office Action has, however, concluded that this is not a function of the Capsid protein but of the entire vector system. While this may be true, there are always additional factors relevant to any function. The importance of this limitation was to exclude Capsid proteins that were incapable of forming particles. The fact that other proteins are involved in the process is irrelevant if the process could fail with certain variants. This is true in even the simplest case. For example, the ability of protein A to bind protein B would presumably constitute a specific functional activity, even protein binding is dependent upon other factors, such as pH, salt concentrations, temperature, etc. It appears that the Examiner's concerns with this claim may be the phrasing "wherein the vector system produces AAV particles." Applicants have therefore amended claim 1 to recite "wherein the capsid protein can form a transducing AAV particle." Support for this amendment is found at least on page 2, paragraph 2 and the paragraph bridging pages 3 and 4 wherein infection, transduction, and tissue tropism are disclosed as dependent upon the capsid protein. Moreover, transduction is both attributable to the capsid protein and easily measured by routine methods.

In addition to the guidance provide by AAV2 deletion studies disclosed on page 2, paragraph 2, the skilled artisan could have aligned the sequence of AAV2 capsid protein (e.g., VP1) to that disclosed for AAV4 in order to determine the conserved regions. This would have guided the artisan to make only conservative mutations within these regions to avoid loss of the common function, i.e., the ability to form particles. In other words, it is the non-conserved

regions that are likely attributable to the unique properties of each capsid protein, such as tissue tropism, and it is the conserved regions that are likely attributable to the common properties, such as the ability to form particles. Thus, written description of this genus of amino acids is satisfied (see Example 11B of the Training Materials).

3. The Office Action has again incorrectly applied caselaw relating to the written description requirement to the instant claims. For example, the Office Action again cites *Fiddes v. Baird* to support the argument that the specification fails to recite a representative number of species defined by structure and function such that the skilled artisan could not envision the claimed compositions. However, the facts in *Fiddes v. Baird* are not applicable to the instant claims. Applicants in *Fiddes v. Baird* claimed a DNA sequence encoding mammalian FGF but only taught a DNA sequences for bovine pituitary FGF. 30 U.S.P.Q.2d at 1481. Thus, neither the applicant nor the skilled artisan could have predicted what sequences would fall within the scope of the genus claim since a representative number of species were not provided to set the metes and bounds of the genus. In contrast, the present application discloses, by reference to the written out sequence, all of the sequences of the components of the claimed vector system. As indicated above, the metes and bounds of this genus are not in question.

Moreover, the Office Action again cites *The Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1566; 43 USPQ2d 1398, 1404 (Fed. Cir. 1997) (hereafter, "*Lilly*") to support the argument that the Applicants are attempting to define the nucleic acid sequences by a statement of function. However, the facts in *Lilly* are not applicable to the instant claims. Applicants in *Lilly* were attempting to claim human cDNA for human proinsulin while only providing the sequence for the rat cDNA. 119 F.3d at 1566; 43 USPQ2d at 1404. As the sequence of human proinsulin was not known at the time that application was filed, the skilled artisan could not know what was actually being claimed. The court therefore concluded that applicants were attempting to claim the coding sequence based only on a indication of what the gene does rather than what it is. In contrast, the present application discloses, by reference to the written-out sequence, all of the sequences of the components of the claimed vector system. It is therefore factually and legally incorrect to assert that the instant claims do not describe the genus by structure.

Applicants therefore respectfully request the withdrawal of this rejection and allowance of claims 2-3, 6-28, and 30-36, and 38-42 and new claim 43.

B. Claims 2-3, 6-28, and 30-36, and 38-42 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled.

The basis for this rejection appears to be two-fold. First, the Office Action asserts that the specification fails to disclose a representative number of species defined by structure and function as indicated in the written description rejection above.

Second, the Office Action asserts that screening variants wherein at least 10% of residues are added, substituted, and/or deleted at random is not routine in the art. For example, the Office Action states that the "applicant fails to point out where in the specification there is support for extensive making and testing of any and all natural and non-natural variants as claimed." Applicants presume that the term "extensive" is meant to refer to the amount of modification being made rather than the skill needed to test for activity, because the Office Action further states "the specification can not be relied on to teach how to make the variants as claimed." However, either conclusion would be erroneous. Applicants are not required to teach methods that are routine in the art, and the Office Action has provided no basis to conclude that the science of amino acid synthesis or nucleic acid recombination is anything other than routine in the art. Likewise, the testing of a particular capsid or Rep variant in a vector system to determine if it produces a transducing particle is no more or less complex than that for a single amino acid mutation. Instead, it appears to be the Examiner's point that the number of modifications necessary to achieve 90% would require "extensive making and testing in order to obtain variants that meet the requirements for the claimed [telomerase activity]." This is neither supported nor the legal standard.

As noted above, the skilled artisan is guided by the specification and knowledge in the art for AAV2 to make modifications to capsid sequence that would result in a transducing particle by 1) conserving residues demonstrated to be important for AAV2 and 2) conserve residues that are consistent between AAV2 and AAV4. Thus, the information available in the art combined with the general predictability for maintaining function at sequence identities above 70% (see Tian, W. and Skolnick, J. J Mol Biol. 2003 Oct 31;333(4):863-82, of record) is such that the

skilled artisan would be able to design a capsid protein having 90% sequence identity to the disclosed sequence for AAV4 capsid that is capable of assembling into a transducing viral particle. The Office Action has not provided any scientific or legal reasoning to contradict this position, but has instead made generalized statements regarding "the unpredictability of a particular area."

Applicants therefore respectfully request withdrawal of the instant rejection and allowance of claims 2-3, 6-28, and 30-36, and 38-42 and new claim 43.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

It is believed that no fee is due with this submission. However, the Commissioner is hereby authorized to charge any fees which may be required to Deposit Account No. 14-0629.

Respectfully submitted,
NEEDLE & ROSENBERG, P.C.

Brian Giles

P. Brian Giles, Ph.D.
Registration No. 57,896

NEEDLE & ROSENBERG, P.C.
Customer Number 36339
(678) 420-9300
(678) 420-9301 (fax)

CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8			
I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.			
Name of Person Mailing (Print/Type)	P. Brian Giles, Ph.D.		
Signature	Brian Giles	Date	6-19-2008